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DRUG DISCRIMINATION: STIMULUS CONTROL DURING REPEATED TESTING IN EXTINCTION

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Rats were trained, under a two-lever drug-discrimination procedure, to respond differentially depending upon whether lorazepam (1.0 mg/kg) or no injection had been administered before the session. Responses on the appropriate lever produced a food pellet under a modified fixed-ratio (FR) 10 schedule, in which the 10 responses had to be emitted consecutively. In reinforcement tests, completing an FR 10 on either lever produced a pellet. In extinction tests, stimulus changes paired with reinforcement occurred but no pellet was delivered. Training sessions were conducted between test sessions. Each of four extinction phases consisted of six tests preceded by one stimulus (e.g., lorazepam). Repeated exposures to extinction reduced response rates for all rats, but stimulus control, as inferred from either percentage of total responses or percentage of total FR 10s on the drug-appropriate lever, remained high. The percentage of total FR 10s measure was less subject to skewing under low-rate conditions than was the percentage of total responses measure and provided an evaluation of stimulus control in terms of meeting the consecutive response contingency. These results demonstrate a level of independence between response rate and stimulus control in drug discrimination, which has positive implications for the validity of interpreting discriminative effects of novel test conditions in well-trained animals, even when overall response rates are low.

Key words: extinction, drug discrimination, stimulus control, lorazepam, lever press, rats

Despite the extensive use of drug-discrimination procedures in behavioral pharmacology, little research exists on the procedural variables used in test sessions (reviewed in Branch, 1991). One such procedural variable in studies with laboratory animals is the use of reinforcers during the testing of discriminative control by drug stimuli. In the most common drug-discrimination procedure, a conditional discrimination is trained between a drug (more precisely, a drug dose) and a no-drug condition using differential reinforcement of food-maintained responding on each of two levers. Discriminative control is established by reinforcing responding on one lever after drug administration and on the other lever when the drug has not been administered. Stimulus control by the drug versus the no-drug condition is demonstrated under test procedures in which the same consequences prevail for responding on either lever. That is, responding on either lever is reinforced (i.e., reinforcement tests) or responding on either lever is not reinforced (i.e., extinction tests) following administration of the training drug dose or vehicle (i.e., placebo). Similarly, tests with different doses of the training drug or other drugs are conducted with nondifferential consequences. Once trained, animals typically serve in a series of drug-discrimination studies.

Choice of testing in reinforcement or extinction has been governed largely by predilections as to which procedure would be more likely to have a deleterious effect on stimulus control of performance in test sessions across repeated testing. A concern about testing under extinction conditions is that if reinforcer delivery does not occur following responding on one lever, a ''win-stay/lose-shift'' contingency might override drug stimulus control of response location. Early in training, this phenomenon does occur and facilitates learning the drug discrimination. Testing under reinforcement conditions has

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been avoided by some because of concern that if reinforcement follows responding on both levers in a test session, stimulus control by the training stimuli will be attenuated in subsequent training sessions and potentially in subsequent test sessions. The drug-discrimination literature suggests, however, that both procedures seem to produce the same qualitative result in terms of test drugs that do or do not share discriminative effects with the training drug stimulus, but one study did show quantitatively different results. In that study, a morphine generalization gradient obtained under a reinforcement test procedure was shifted to the left of that obtained under an extinction test procedure (Kaempf & Kallman, 1987).

The extent to which stimulus control generated by the training sessions can be overridden by reinforcement variables during test sessions has received little systematic attention. Rijnders, Jarbe, and Slangen (1990), however, studied the effects of repeated extinction test sessions on stimulus control under a chlordiazepoxide versus placebo discrimination. Rats were trained on a tandem variable-interval (VI) 40-s fixed-ratio (FR) 10 schedule of food delivery during 10-min training sessions. During one session each week, a 2-min extinction period was followed by 8 min of regular training. Generalization testing was conducted in 2-min extinction sessions twice per week. The resistance of discriminative accuracy to extinction was tested during a phase in which consecutive 2-min extinction sessions, preceded by either chlordiazepoxide or saline injection, were conducted for 30 sessions or until there were less than 10 responses on either lever for three consecutive sessions, whichever occurred first. Stimulus control remained high throughout the extinction-testing phase even though response rates decreased. The procedures used by Rijnders et al. may have promoted substantial resistance to extinction of discriminative accuracy though, because 2-min periods of extinction had been followed periodically by periods of reinforcement throughout training and the initial generalization-testing phase.

In our laboratory, drug stimulus generalization testing has been carried out in reinforcement conditions with both rats and baboons. The response requirement has been a modified FR schedule in which the required number of responses had to be made consecutively on one lever to produce food-pellet delivery (e.g., Ator & Griffiths, 1999). Drug stimulus control seemed unusually strong under these training conditions. When ''extinction'' was imposed inadvertently in a training session by programming reinforcer delivery on the ''inappropriate lever,'' experienced subjects often stopped responding on the appropriate lever without ever switching levers and thereby coming in contact with the programming error (observations summarized in more detail in Ator, 1990).

Ator (1990) followed up on the unplanned extinction tests by using limited exposure to probe sessions to test the effect of extinction in animals with lengthy histories of testing only in reinforcement. The probe sessions were the same length (20 min) as the regular training and test sessions. In a probe session preceded by the training dose of lorazepam and one preceded by placebo, no consequence was programmed for responding on either lever. In two other such probe sessions, the usual ''postpellet'' timeouts occurred after the response requirement was met on either lever. In all these tests, 75% to 80% of the total responses were on the lever appropriate to the injection that preceded the test in the majority of rats. These results suggest that once trained, control by the drug stimulus was prepotent and that a win-stay/lose-shift pattern was not readily adopted even under conditions in which extinction-induced variability in responding could be expected to occur.

A reduction in response rate is the other usual effect of prolonged or repeated exposure to extinction. It can occur during the first exposure to extinction if the session is long enough, or it can occur across sessions with repeated exposure to extinction (Bullock, 1960; Bullock & Smith, 1953; Clark & Taylor, 1960; Wickens & Miles, 1954; Zarcone, Branch, Hughes, & Pennypacker, 1997). Low response rates as a function of repeated testing in extinction have implications for interpretation of stimulus control in drug-discrimination procedures. A common assumption in drug-discrimination research is that percentages of responding on one lever versus another are uninterpretable in terms of stimulus control when response rates are very low.

The concern most often arises when response rates are low following high drug doses. One interpretation (albeit circular) has been that ''toxic'' effects of the drug (i.e., evidenced by low response rates) override stimulus control and result in random responding. For this reason, a minimum response requirement commonly is imposed for interpreting lever-selection data (e.g., that the usual minimum number of responses required for reinforcer delivery have been made). Even in that context, however, stimulus control results are prone to be interpreted differently when response rates are reduced in a test session than when they are not. This implies that lever selection and response rate are not believed to be independent of each other as dependent variables.

Studying lever selection separately from rate is difficult in a free-operant procedure because a single response can have a large effect on percentage of total responses when response rates are very low. Observations in our laboratory suggest that when the reinforcement contingency requires that multiple responses be made consecutively, percentages of total ratios completed on a particular lever may be more meaningfully interpreted in terms of stimulus control when overall response rates are extremely low. The present study was designed to use such a measure, compared to the more common percentage of total responses on the training-drug-appropriate lever, to follow up and extend the observations of Rijnders et al. (1990) and Ator (1990) on stimulus control of drug discrimination during extinction. Unlike the study by Rijnders, here each of the multiple extinction tests was to be interpolated between pairs of training sessions in which criterion level performance was demonstrated, which is how drug generalization testing typically is conducted. Unlike the study by Ator, here each rat was to be exposed to multiple extinction tests until rate of responding in those test sessions was consistently low. If stimulus control by the training conditions remained strong during repeated testing in extinction, it would provide support for viewing response rate and lever choice in drug-discrimination test sessions independently even when response rates are very low.

METHOD

Subjects

Six male Long-Evans hooded rats (Harlan Sprague-Dawley) were housed individually with a 12:12 hr light/dark cycle (lights on at 7:00 a.m.). Weights were held stable at 330 ± 10 g with daily rations of commercial laboratory rat chow (20 to 30 min after experimental sessions). The rats had been obtained at 6 weeks of age and trained to discriminate lorazepam 1.0 mg/kg from vehicle under the drug-discrimination procedure described below. Before the present experiment, generalization gradients for lorazepam, diazepam, imidazenil, and pentobarbital had been characterized over an 8-month period using the testing-in-reinforcement procedure described below.

Apparatus

Six custom-made operant conditioning chambers were used. Each rat was trained and tested in the same chamber throughout the study. The chamber specifications have been described by Ator (1991a; photo in Ator, 1991b). Briefly, two rodent levers were mounted 13 cm apart on one wall. Identically colored jewel lights were mounted on the wall, one above each lever. A food cup, into which an electromechanical feeder delivered 45-mg Noyes food pellets, was centered on the chamber wall opposite the levers. White noise and a ventilation fan in a larger sound-attenuating enclosure masked extraneous sounds. The control of experimental events and collection of behavioral data were accomplished with an IBM-compatible computer, solid-state chamber interface cards, and MED-PC® State Notation software. Lever presses and feeder operations were monitored with an event recorder (Esterline-Angus).

Drug Administration

The training drug (lorazepam), dose (1.0 mg/kg), route of administration (intraperitoneal [i.p.] injection), and time between injection and the beginning of the opportunity to respond under the food reinforcement schedule (60 min) were the same as in the probe sessions reported by Ator (1990). Lorazepam was dissolved in a vehicle of propylene glycol (80%) and polyethylene glycol 400

(20%), which then was diluted 1:1 with 0.9% saline. Lorazepam stock solution without saline was maintained for up to 30 days. Once diluted with saline, the solution was discarded after 7 days. For placebo injections, the lorazepam vehicle (i.e., the solvent diluted with saline) was injected. Injection volumes were 1 ml/kg. Once weighed and injected, the rat was returned to the home cage for the first 45 min of the 60-min interval before the session.

Procedure

Training sessions. Rats were trained to discriminate 1.0 mg/kg lorazepam from a no-drug condition using the left and right levers under procedures like those described by Ator (1990). Each experimental session was preceded by a 15-min timeout, during which the chamber was dark and lever presses were recorded but had no programmed consequences. At the end of the 15-min timeout, the jewel lights were illuminated and pellet delivery depended upon completion of 10 consecutive responses on the lever appropriate to the drug or no-drug training condition in effect. Changing from one lever to the other lever reset the response requirement of FR 10 for the initial lever. A 10-s timeout, like the presession timeout, followed each pellet delivery. Whether the left or right lever was paired with pellet delivery after lorazepam administration was counterbalanced across subjects. Rats 42-2, 42-4, and 42-6 were assigned the left lever as the lorazepam-appropriate lever, and Rats 42-1, 42-3, and 42-5 were assigned the right lever as the lorazepam-appropriate lever. Sessions were 20 min in duration and were conducted Monday through Friday. Lorazepam and no-drug training sessions always alternated, except as described below. No-drug training sessions were conducted without being preceded by vehicle injections, because the injection procedure does not appear to serve as a basis for drug/no-drug discrimination under a two-lever procedure in rats (Ator & Griffiths, 1989, 1999; Overton, 1979).

Before any testing of these rats for the present experiment, performance had to meet the following criteria in four consecutive drug (D) and no-drug (ND) training sessions (either a D ND D ND or an ND D ND D sequence). The criteria were that (a) at least 95% of all responses in a session had to occur on the appropriate lever and (b) no more than nine consecutive responses on the inappropriate lever could occur before the first pellet delivery of the session.

Reinforcement test sessions. Reinforcement test sessions were conducted to demonstrate control of response location by lorazepam and its vehicle, before and after testing in extinction. The rat was weighed and then injected with either lorazepam or its vehicle and returned to the home cage for 45 min, after which it was placed in the experimental chamber for the 15-min presession timeout. These test sessions were identical to training sessions except that making 10 consecutive responses on either lever produced a food pellet. As in training sessions, any response on the alternate lever prior to completing the FR 10 reset the response requirement for both levers. Rats were tested twice with lorazepam and twice with vehicle before and after the extinction-testing phase of the experiment (exceptions given in the Results). If a rat did not contact the contingency that pellets were available for responding on either lever in a test session, then the very next session was also a test session. If a rat contacted that contingency, training sessions (D ND or ND D) were conducted before the next test session to assess criterion-level performance. If criterion-level performance did not occur in any training session, training continued until it occurred in four consecutive training sessions.

Extinction test sessions. Extinction test sessions were identical to reinforcement test sessions except that the tube that delivered food pellets from the feeder to the food cup was displaced into a small beaker behind the panel. Thus, 10 consecutive responses on either lever produced feeder operation and a 10-s timeout, but no food pellet. At least two training sessions were conducted between extinction test sessions. The order of training sessions between test sessions was counterbalanced so that D and ND training sessions preceded test (T) sessions equally often (i.e., ND D T D ND T ND D T etc.). If criterion performance did not occur in a training session, then the next test session could not occur until criterion performance occurred in four consecutive training sessions.

There were two types of extinction test

phases: ones in which test sessions were preceded by vehicle injections and ones in which test sessions were preceded by lorazepam injections. Each extinction test phase included at least six extinction tests. Order of exposure to the two types of test phases was counterbalanced: Rats 42-1, 42-2, and 42-3 were exposed to the vehicle extinction test phase first and the lorazepam extinction test phase second, and Rats 42-4, 42-5, and 42-6 were exposed to those phases in the opposite order. The sequence then was replicated for each group of rats.

Data Analysis

Responses during the time the jewel lights were turned on, which excluded timeout periods, were used to calculate response rates, percentages of total responses, and percentages of total ratios completed on each lever. Percentage of total responses on the lorazepam-appropriate lever was plotted regardless of whether 10 consecutive responses were completed on one lever. Percentages of total ratios on the lorazepam-appropriate lever were not plotted if no ratio was completed on either lever because the criterion for reinforcement (i.e., 10 consecutive responses) had not been met. Although responding on either lever is appropriate in test sessions, the terminology of appropriate and inappropriate lever relative to the type of presession injection is retained to facilitate the description of results.

Stimulus control in test sessions was defined differently from criterion performance in training sessions. The definition is consistent with the convention in the drug-discrimination literature and is appropriate to testing in a two-choice conditional discrimination (Sidman, 1980). That is, stimulus control in test sessions was not interpreted as meaningfully different from performance that met criterion in training sessions if 80% or more of total responses were allocated to the lever appropriate to the stimulus being tested (i.e., lorazepam or its vehicle).

RESULTS

Response Rates

Figure 1 shows response rates on each lever across consecutive test sessions under reinforcement and extinction conditions. Each graph shows data for 1 rat. The column of graphs on the left shows data for rats that received the vehicle stimulus first, and the column of graphs on the right shows data for rats that received the lorazepam stimulus first. In reinforcement test sessions, both before and after the four extinction test phases, response rates on the lever appropriate to the presession injection were approximately one response per second or more for most rats, regardless of whether lorazepam or vehicle was injected. During reinforcement test sessions, all rats except Rat 42-6 responded on the inappropriate lever but at a rate 10 to 100 times lower than response rates on the appropriate lever. Rats 42-1, 42-4, and 42-5 responded on the inappropriate lever in reinforcement test sessions only in those sessions preceded by lorazepam injection and not in those preceded by vehicle.

In the first extinction test session, response rates on the appropriate lever decreased below those in the reinforcement test phase, regardless of whether the test session was preceded by lorazepam or vehicle. Responding on the inappropriate lever occurred in the first extinction test session except for Rat 42-6, but was 10 to 100 times lower than response rates on the appropriate lever for most rats. Response rates on the appropriate lever continued to decrease across test sessions in the first extinction phase, if only slightly for some rats, and were below 0.1 response per second by the sixth extinction test session. Response rates on the inappropriate lever did not show a monotonically increasing or decreasing trend; they were zero in one or more extinction test sessions for each rat.

The presession injection was changed for the second extinction phase to lorazepam for Rats 42-1, 42-2, and 42-3 and to vehicle for Rats 42-4, 42-5, and 42-6. In the first extinction test session, response rates on the appropriate lever remained higher than response rates on the inappropriate lever. Response rates on the appropriate lever did not show a monotonically decreasing trend across the remaining extinction tests for this phase. Response rates on the inappropriate lever increased during this phase and were sometimes equal to response rates on the appropriate lever.

The two types of extinction phases were replicated by reversing the type of presession

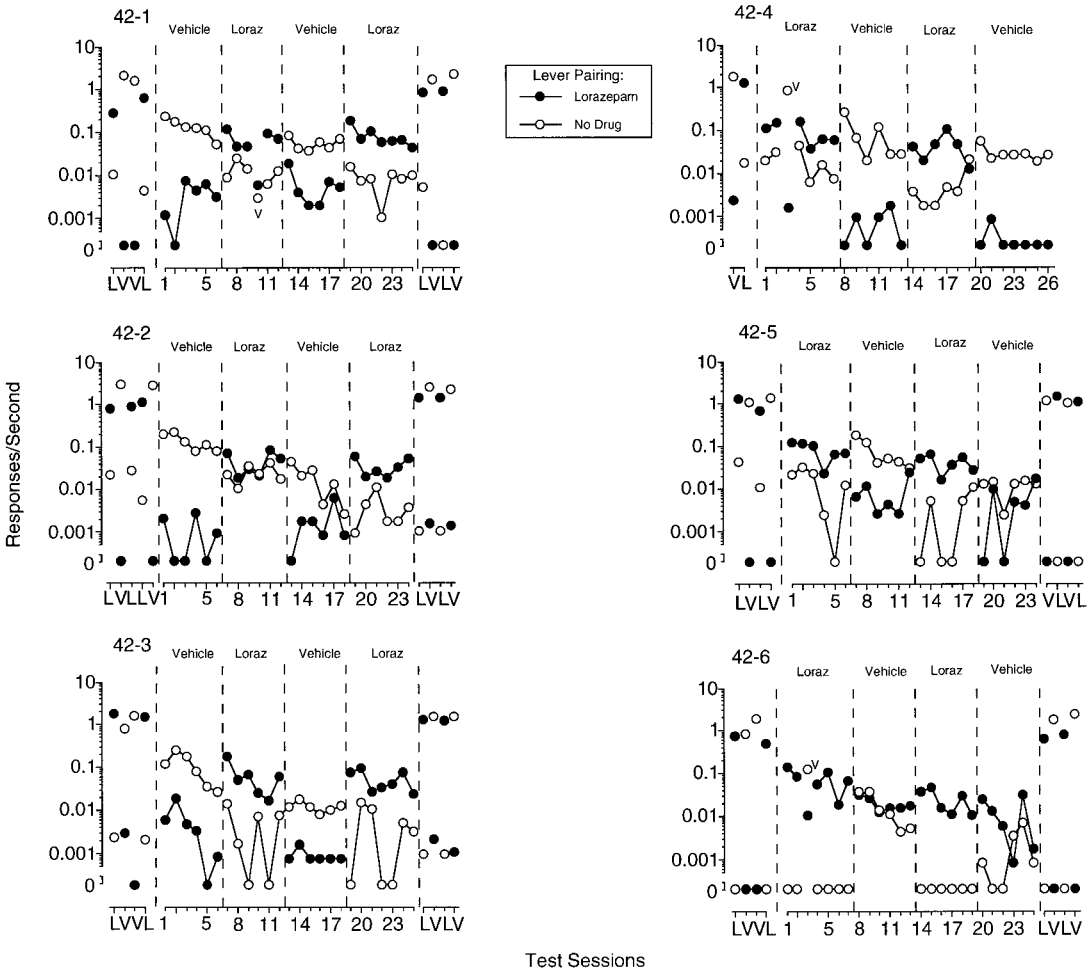

Fig. 1. Responses per second for both levers across consecutive test sessions that were preceded by an injection of either lorazepam 1.0 mg/kg (L) or its vehicle (V) 60 min before the test for each rat trained to discriminate lorazepam 1.0 mg/kg from the no-drug condition. The test results over the Ls and Vs on the *x* axis are for reinforcement tests, and the test results over the numbered segment of the *x* axis are for the four extinction test phases. At least two training sessions were interpolated between test sessions. Closed circles represent responding on the lever for which responding had been reinforced with food pellets when lorazepam preceded training sessions. Open circles represent responding on the lever for which responding had been reinforced with food pellets when no injection preceded training sessions. Note that the *y* axis is a log scale. Zero has been added to be able to indicate that no responses occurred during the session. The V next to the symbols in the first extinction phase for Rats 42-4 and 42-6 and in the second extinction phase for Rat 42-1 indicate that, by mistake, vehicle was administered prior to the test session instead of lorazepam. Rat 42-4 was not tested in reinforcement following the extinction test phases due to illness.

injection twice more. Response rates on the appropriate and inappropriate levers did not decrease further. In replication sessions preceded by lorazepam, response rates on the appropriate and inappropriate levers were similar to what they had been in the first lorazepam phase for most rats. The response rate of Rat 42-2 on the inappropriate lever decreased compared to the first lorazepam extinction phase so that it did not overlap rates on the appropriate lever.

In replication sessions preceded by vehicle, response rates on the appropriate lever remained higher than response rates on the inappropriate lever as they had in the initial exposure to this type of extinction session for Rats 42-1, 42-3, and 42-4. Rats 42-2, 42-5, and 42-6 showed a convergence of response rates

on the appropriate and inappropriate levers, which replicated the convergence observed during vehicle extinction sessions for Rats 42-5 and 42-6. Also in the vehicle replication phase, those rats that were first exposed to extinction in sessions preceded by vehicle in Phase 1 (Rats 42-1, 42-2, and 42-3) showed a decrease in the number of sessions without a response on the inappropriate lever. Two of the 3 rats that were first exposed to extinction in sessions preceded by lorazepam and exposed to vehicle extinction sessions in Phase 2 (Rats 42-4 and 42-5), however, showed an increase in the number of sessions in which they failed to respond on the inappropriate lever. Rat 42-6, on the other hand, showed the greatest breakdown in stimulus control in the vehicle replication phase. That is, response rates on the appropriate lever were below those on the inappropriate lever in the first three sessions, and then rates on the two levers converged for the remainder of that phase.

Percentages of Lorazepam-Appropriate Responses and FR 10s Completed

Figures 2 and 3 show, respectively, the percentage of responses on the lorazepam-appropriate lever and the percentage of FR 10s completed on the lorazepam-appropriate lever across test sessions. During reinforcement tests with presession lorazepam injections, the rats made at least 96% of their responses and completed virtually 100% of their FR 10s on the lorazepam-appropriate lever. Presession vehicle injections occasioned less than 1% of responses on the lorazepam-appropriate lever, and no FR 10s were completed.

In the first extinction test session, presession vehicle injections occasioned less than 10% of responses on the lorazepam-appropriate lever. Presession lorazepam injections occasioned greater than 80% of responses on the lorazepam-appropriate lever. No rat completed an FR 10 on the inappropriate lever in the first extinction test session. In the remaining five extinction tests of the first phase, rats in the vehicle group emitted fewer than 10% of their total responses and completed no FR 10s on the lorazepam-appropriate lever. Rats in the lorazepam group emitted 79% or more of their responses and completed all of their FR 10s on the lorazepam-appropriate lever, with the exception of two sessions at 90% (Rat 42-4, Session 4, and Rat 42-5, Session 2). Two rats from the lorazepam group were inadvertently injected with vehicle during the first extinction test phase (Rat 42-4, Session 3, and Rat 42-6, Session 3). Responding in those sessions was exclusively on the no-drug-paired lever for Rat 42-4 and less than 20% on the lorazepam-appropriate lever for Rat 42-6.

Changing the presession injection for the second phase to lorazepam for Rats 42-1, 42-2, and 42-3 and to vehicle for Rats 42-4, 42-5, and 42-6 decreased stimulus control compared to the first phase, as interpreted from the percentage of lorazepam-appropriate responding measure. In sessions preceded by lorazepam in the second phase, lorazepam-appropriate responding was below 80% for one or more sessions for all 3 rats. Percentage of total FR 10s completed was below 100% in only four of the nine sessions in which percentage of total responding was below 80%, however. In sessions preceded by vehicle, lorazepam-appropriate responding was below 20% for Rats 42-4 and 42-5, except for the last session of this phase for Rat 42-5. All test sessions resulted in greater than 20% lorazepam-appropriate responding for Rat 42-6. Percentage of completed FR 10s also was less than 20% for Rats 42-4 and 42-5, except for the last session for Rat 42-5. Only one test session resulted in less than 20% of completed FR 10s for Rat 42-6.

When the lorazepam extinction phase was replicated, lorazepam-appropriate responding was above 80% in all six sessions for 2 rats (Rats 42-3 and 42-6) and in the first five sessions for 2 rats (Rats 42-4 and 42-5), which was similar to performance in the first phase of lorazepam extinction tests. Rats 42-1 and 42-2 also emitted greater than 80% lorazepam-appropriate responding during five or six of the lorazepam extinction replication sessions, but this was an increase compared to the first phase of lorazepam extinction tests. When the vehicle extinction phase was replicated, lorazepam-appropriate responding did not exceed 20% for Rats 42-1, 42-3, and 42-4, which was similar to performance in the first phase of vehicle extinction tests. Rat 42-2's percentages of lorazepam-appropriate responding increased across the six tests, however, and Rats 42-5 and 42-6 continued a pattern of increased lorazepam-appro-

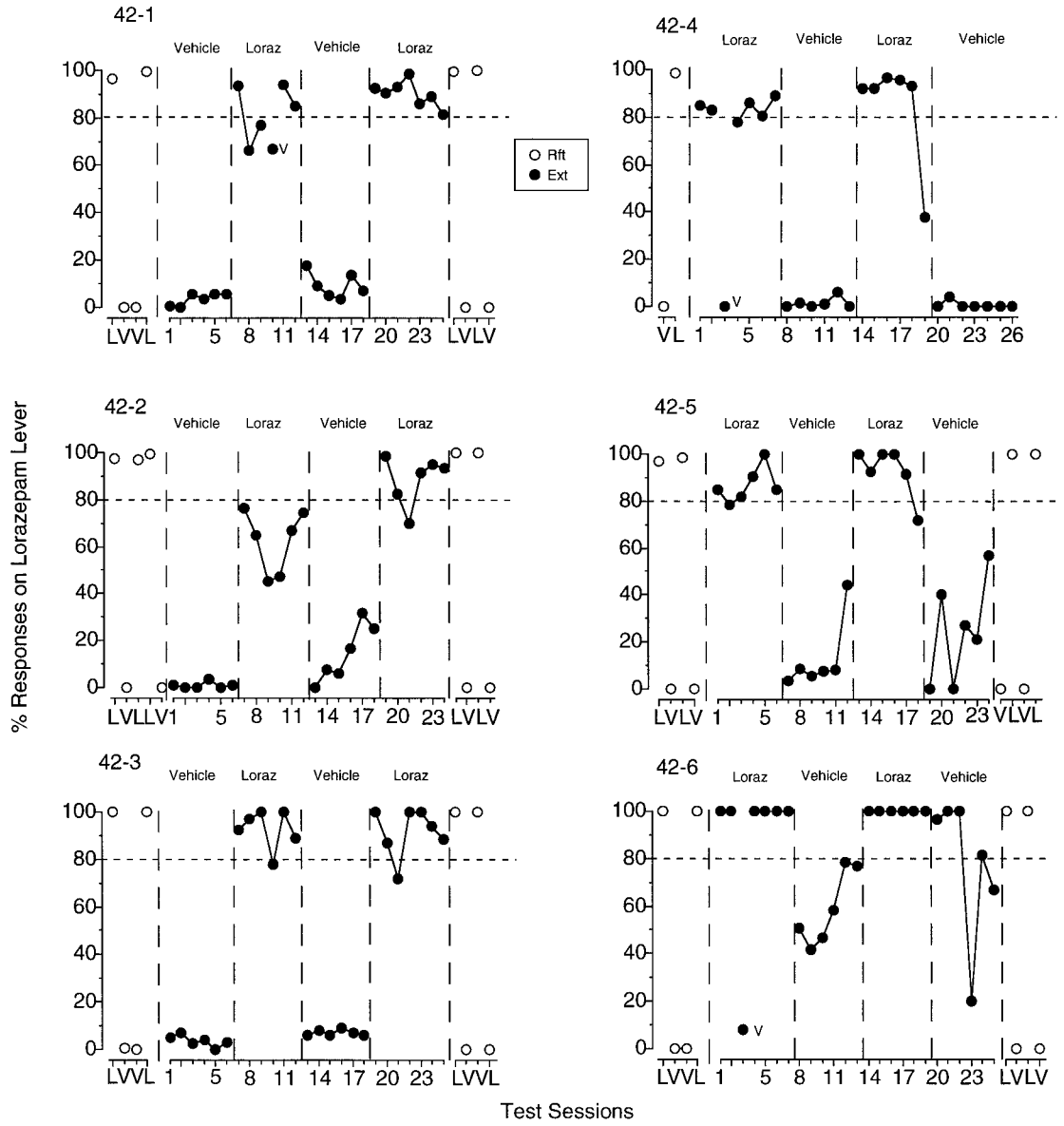

Fig. 2. Percentage of total test-session responses that were on the lorazepam-appropriate lever across consecutive reinforcement and extinction test sessions for each rat. Open circles indicate test sessions in which the food-pellet reinforcer was delivered when 10 consecutive responses were completed on either lever. Filled circles indicate test sessions in which only the sound of the feeder and the timeout followed completion of the response requirement. Other details as in Figure 1.

priate responding after vehicle injections, which began during their initial exposure to the vehicle extinction phase.

The percentage of completed FR 10s measure showed more evidence of stimulus control by the training conditions during the replications than did the percentage of lorazepam-appropriate responses measure. After lorazepam injections, the percentage of FR 10s completed on the appropriate lever was 100% in all except three test sessions, and it was below 80% in only two test sessions (one each for Rats 42-4 and 42-5). Likewise, percentage of FR 10s completed after vehicle injections was greater than 20% in only two test sessions (both for Rat 42-5) for 5 of the

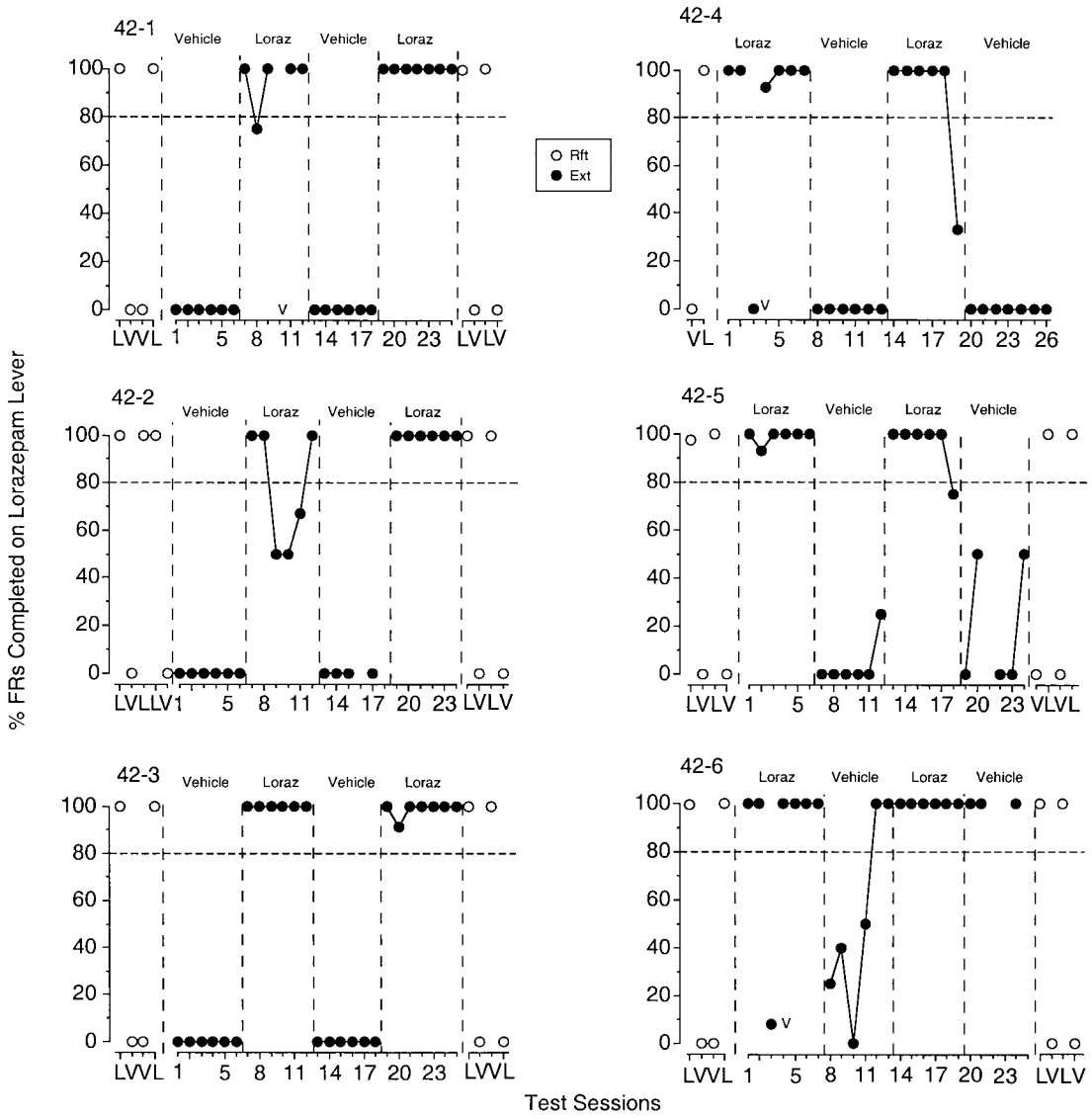

Fig. 3. Percentage of completed 10-consecutive-response ratios (FR 10s) on the lorazepam-appropriate lever across consecutive reinforcement and extinction test sessions for each rat. Open circles indicate reinforcement test sessions in which the food-pellet reinforcer was delivered when the FR 10 was completed on either lever. Filled circles indicate extinction test sessions in which only the sound of the feeder and the timeout followed completion of the FR 10. Data points were omitted if no FR 10 was completed on either lever because 0% lorazepam-appropriate FR 10s implies that 100% FR 10s were completed on the other lever. Other details as in Figure 1.

6 rats. For Rat 42-6, the percentage of completed FR 10s measure reveals that stimulus control was disrupted, as all of the completed ratios were on the lorazepam-appropriate lever after vehicle injections. The percentage of FR 10s measure also reveals that after vehicle injections, Rats 42-2, 42-5, and 42-6 sometimes did not complete a single FR 10 (symbols are omitted for these sessions).

DISCUSSION

As is characteristic of behavior during extinction, response rates on the appropriate lever in the present study decreased, and, for the majority of rats, responding on the inappropriate lever increased in extinction compared to reinforcement test sessions. Most of the decrease in response rates on the appro-

priate lever occurred within the first few extinction test sessions. Response rates on the appropriate lever either slightly decreased further or were relatively stable throughout the remainder of the approximately 24 extinction test sessions. The extent of the decrease in response rates was the same for the tests preceded by lorazepam and the tests preceded by vehicle. Response rates typically were 10 times higher on the appropriate lever than on the inappropriate lever, which indicated continuing control of response location by the lorazepam stimulus. On the other hand, response rates on the two levers converged in some phases, which would be interpreted as a loss of control by the lorazepam stimulus. In the drug-discrimination literature, however, response rates on the individual levers typically are not used as the measure of stimulus control, although they often are averaged and evaluated as a measure of the drug's effect on overall response rate (Stolerman, 1993).

The percentage of total test-session responding that is on the drug-appropriate lever is commonly used as the measure of stimulus control (Stolerman, 1993). If the percentage is 80% or greater, the test stimulus is not considered meaningfully different from the drug training stimulus. Conversely, if the percentage is 20% or less, the test stimulus is considered completely different from the drug training stimulus. By this criterion, responding was not qualitatively different from the analogous training session in most of the first extinction test phase, regardless of whether vehicle or lorazepam injections preceded the test session. During the second extinction phase, rats showed more variable stimulus control than they had in the first phase. Stimulus control, however, did not progressively deteriorate across phases. Rather, percentage of lorazepam-appropriate responding in the replication tests preceded by lorazepam was 80% or more in all or all but one extinction test session. Percentage of lorazepam-appropriate responding in the replication tests preceded by vehicle, however, was above 20% in two or more extinction test sessions for half the rats.

Myerson and Hale (1988), using exteroceptive discriminative stimuli, reported that response distributions established during concurrent reinforcement training were maintained throughout extinction, and that the observed variability in later extinction sessions may have resulted from comparison of smaller behavioral samples. In the present study, response distributions increased in variability in terms of ''percentage of inappropriate responses'' when comparing the standard deviations for the first two phases of extinction (Phases 1 and 2, $M = 12\%$, $SD = 7\%$) to the last two phases (Phases 3 and 4, $M = 11\%$, $SD = 10\%$). A comparison of the absolute number of inappropriate responses between the first two and last two extinction phases shows a decrease in variability (Phases 1 and 2, $M = 11$, $SD = 8$; Phases 3 and 4, $M = 5$, $SD = 4$). Thus when response rates decrease in drug-discrimination procedures, whether due to extinction or to a high dose of drug, increased variability in the percentage of responses measure is at least partially a product of the percentage calculation itself.

The percentage of FR 10s completed measure showed the least disruption of stimulus control by the extinction test procedure. Even though some responding on the inappropriate lever occurred, as shown by the response rate and percentage of lorazepam-appropriate responding measures, the percentage of FR 10s completed was 100% on the appropriate lever in many of those sessions. These rats had extensive experience with testing in reinforcement, in which pellets were sometimes obtained by responding on either lever in the same test session (Ator & Griffiths, 1999). Yet during the first phase of extinction tests, only half the rats completed a response requirement on the inappropriate lever (albeit in only one session), and the percentage of FR 10s completed on the appropriate lever did not decrease below 80%. The percentage of FR 10s completed was less influenced by small changes in the distribution of responses. For that reason it was a better indicator of continued stimulus control of the reinforced operant class (which was 10 consecutive responses on one lever) when response rates were low than was the response rate or percentage of lorazepam-appropriate responding measure.

The percentage of completed FR 10s measure is not commonly reported in drug-discrimination research, but some laboratories commonly report some form of ''lever selection'' measure. For example, the percentage

of rats that complete the response requirement on the drug-appropriate lever prior to the first reinforcer of the session is referred to as the percentage of rats that ''select'' that lever (review in Stolerman, 1991). Also, it is common for laboratories not to report the percentage of completed responses measure for a given animal if insufficient responses were emitted to produce the reinforcer, which may be characterized as failure to make a ''lever choice.'' In the present study, the percentage of reinforced ratios measure can be seen as analogous to a lever selection measure in which lever selection was defined as completion of 10 consecutive presses on one lever.

The percentage of completed FR 10s measure also indicated that for some rats, the vehicle injection itself became discriminative for extinction. After the first phase of vehicle extinction tests, rats sometimes failed to complete 10 consecutive responses on either lever after vehicle. This likely was due to the fact that the no-drug training sessions were not preceded by vehicle injection. If the failure to complete an FR 10 in some of the later vehicle sessions was due to the development of an S^{Δ} function for the vehicle injection, it bears further investigation, given that the injection occurred 45 min before the rat was placed in the chamber for the presession timeout and given Overton's (1979) extensive work showing a failure of vehicle injections to gain discriminative control of responding.

In the present study, only the reinforcer was removed, leaving the other stimuli (10-s timeout and feeder operation) that accompanied reinforcer delivery intact. One effect of continuing to present the stimuli that accompanied pellet delivery may have been to maintain responding longer during extinction. In the present study, all rats continued to respond across the four extinction test phases, despite repeated experience with the omission of pellet delivery. To understand how control by drug or other discriminative stimuli is affected by extinction, the reinforcer and the stimuli that accompany the reinforcer should be examined independently.

A common assumption in the drug-discrimination literature is that percentage of responding on a particular lever is uninterpretable in terms of drug stimulus control when response rates are very low. The data from the present experiment illustrate the relative independence of the response rate and lever choice measures. Although response rates decreased substantially, the distribution of responses and completed FR 10s across levers indicated that stimulus control of lever choice by the training conditions remained reliable. These data suggest that distributions of responding across levers under novel test conditions may indeed be interpretable in terms of the discriminative stimulus effects of the test drug even when response rate is low. This interpretation is consistent with the findings of Kaempf and Kallman (1987). They did not find qualitative differences in morphine generalization when they compared a gradient obtained under extinction test conditions with one obtained under reinforcement test conditions. Both testing conditions yielded gradients that showed full generalization. Instead, a quantitative difference in the gradients occurred: More responding occurred on the drug-appropriate lever at lower morphine doses under reinforcement test conditions. Future research could be well directed to investigating the generality of this finding.

Questions about interpretation of generalization data in the context of low overall response rates more often arise, however, when low response rates are seen as a function of the direct effects of the drug dose being tested. Although the present data support the view that ''lever choice'' data measure a different aspect of behavior than overall response rate, they do not address the question of direct effects of drugs on stimulus control processes generally. One potential strategy would be to deliver rate-decreasing doses prior to sessions in which differential responding is under the control of exteroceptive stimuli, such as tones or lights. A number of studies of stimulus control under free-operant and discrete-trial procedures have studied the effects of psychoactive drugs on stimulus control (review by Katz, 1990). Katz concluded that ''changes in stimulus control of responding contributed little if anything to the changes in rates and patterns of schedule-controlled responding'' (1990, p. 32). Exceptions were found with some drugs under some conditions as a function of, for example, whether the procedure was free operant or discrete trial and whether the degree of

stimulus control under baseline conditions was less than optimal. Further research into such variables is needed with respect to drug discrimination to understand how procedural variables and baseline levels of stimulus control contribute to assessments of drug stimulus control when low response rates are a function of drug dose.

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